Advances in Understanding the Mechanism of Ophthalmic Viscosurgical Device Retention in the Anterior Chamber or on the Corneal Surface during Ocular Surgery

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Retention durability, especially in the eye, is one of the most important properties of ophthalmic viscosurgical devices (OVDs) during ocular surgery. However, the information on the physical properties of OVDs is insufficient to explain their retention durability. The purpose of this study is to clarify the mechanism of OVD retention to improve understanding of the behavior of OVDs during ocular surgery. To elucidate the mechanism of OVD retention, we have developed a new test method for measuring repulsive force. As a result, the maximum repulsive force of OVDs was positively and well correlated with the retention durability of investigated OVDs. Consequently, we demonstrated that the repulsive force could be used as an index of retention durability on the ocular surface and in the eye. We directly compared the intraocular retention durability of three OVDs (Shellgan, Viscoat, and Opegan-HI) in ex vivo porcine eyes. Opegan-HI was immediately removed from the anterior chamber, but Shellgan and Viscoat remained largely in the anterior chamber as determined by fluorescence imaging. These results showed that the intraocular retention behavior of OVDs was similar to their ocular surface behavior in our previous report, suggesting that retention durability is dependent on the OVD itself. The retention durability of Shellgan seemed to be higher than that of Viscoat, and the maximum repulsive force of Shellgan was 1.35-fold higher than that of Viscoat. Therefore, the repulsive force might be a useful index for assessing the difference in the retention durability between OVDs such as Shellgan and Viscoat.

Key words ophthalmic viscosurgical device (OVD); repulsive force; adhesive property; retention durability; ocular surgery; Wet Shell Technique

Introduction

Healon, 1% sodium hyaluronate (HA), was first viscoelastic substance introduced in cataract surgery in 1979.3 Since then, HA products have contributed to technological innovation in cataract surgery as ophthalmic viscosurgical devices (OVDs). Various OVD products using HA with different rheological properties are commercially available, and they are mainly classified into cohesive and dispersive types based on their cohesion-dispersion index.2) Cohesive OVDs containing a high molecular weight HA, such as Healon, help maintain the anterior chamber space during surgery due to their highly viscous with non-Newtonian flow properties. However, under turbulent conditions caused by procedures like phacoemulsification and aspiration (PEA) or irrigation aspiration (IA), such cohesive agents tend to congeal and be pushed out of the eye as a single mass.3) Compared with cohesive OVDs, dispersive OVDs such as Viscoat and Shellgan, which are combination products containing 3% HA and 4% chondroitin sulfate (CS), tend to adhere strongly to tissue, resulting in greater corneal endothelium protection even under turbulent conditions, and are less removable from the anterior chamber due to their adhesive nature.4,5)

Generally, corneal dryness during ocular surgery increases the risk of corneal epithelial damage and reduces the visibility of the surgical field for surgeons.6) Many surgeons, therefore, use OVDs as corneal wetting agents to prevent such risks during ocular surgery. This procedure is commonly termed the “Wet Shell Technique” in Japan.7,8) Dispersive OVDs are the preferred corneal wetting agents because of their higher adhesiveness and retention durability on the corneal surface than cohesive OVDs.3–10)

Ophthalmic researchers have concluded that retention durability is one of the important properties of OVDs during ocular surgery not only in the intraocular space but also on the ocular surface.9,10) Previously, we have demonstrated that OVD products have their own rheological properties, even if their product specifications are the same value.11,12) We have considered that rheological properties, which are not estimated so far, might also influence the retention durability of OVDs not only on the corneal surface but also in the eye. In the latest study, we have developed a method for evaluating the retention durability of OVDs on the corneal surface and demonstrated that Shellgan and Viscoat have suitable retention durability as corneal wetting agents.13) Furthermore, to understand the retention mechanism, we have focused on one of the adhesive properties of OVDs, tack, which is defined as the force needed to separate an adhesive from a surface after light contact under light pressure. We have developed a method for determining the detachment force (or tack) of OVDs using a texture analyzer.14,15) However, we could not base the difference...
in retention durability on the corneal surface between Shellgan and Viscoat only on detachment force.

In this study, to better understand the retention durability of OVD during ocular surgery, we have developed a new measurement method to evaluate the repulsive force of OVD by reference to the gel strength testing. Measuring the repulsive force of each OVD deepened our understanding of the rheological properties of OVDs. In particular, it was useful for understanding the difference in intraocular retention behavior between Shellgan and Viscoat.

**Experimental**

OVDs The dispersive OVD products Opegan®, Opegan-Hi®, Shellgan®, Oplead®, Viscoat®, and Discovisc® were purchased from the distributors shown in Table 1. A 3% hyaluronic acid (HA) solution was prepared from HA powder (derived from chicken combs, Seikagaku Corp., Tokyo, Japan) as previously reported. All OVDs shown in Table 1 were evaluated maximum repulsive force, and Opegan-Hi, Shellgan, and Viscoat were evaluated removability from the porcine anterior chamber by methods described below.

Removability of OVDs from the Porcine Anterior Chamber during the Aspiration To visualize Opegan-Hi, Shellgan, and Viscoat without changing their apparent viscosity, these OVD products were stained by fluorescein sodium (0.7 mg, AYUMI Pharmaceutical Corp., Tokyo, Japan). The resulting OVD (250 μL) was injected into a fresh porcine eye harvested on the day by Agris-One Corp. (Saitama, Japan). The injected OVD was aspirated by using a pulsed electrical activity (PEA) device (Phacompo®, Allergan/Optical Micro Systems, MA, U.S.A.) with an IA chip or PEA chip attached, which was placed in the center of the anterior chamber without movement for 60 s and moved for 60 s. IA was performed under the following conditions: flow rate, 26 mL/min; vacuum pressure, 120 mmHg; ultrasound output, 30%; bottle height, 70 cm. PEA was performed under the following conditions: flow rate, 24 mL/min; vacuum pressure, 500 mmHg; bottle height, 70 cm. PEA was performed under the following conditions: flow rate, 24 mL/min; vacuum pressure, 120 mmHg; ultrasound output, 30%; bottle height, 60 cm. During the aspiration, the anterior chamber was irrigated with a BSS® plus (Alcon Inc., Hünenberg, Switzerland).

**Measurement of Maximum Repulsive Force** Repulsive force of each OVD was measured with a texture analyzer (Stable Micro Systems, Surrey, U.K.) equipped with a cylindrical perspex probe (25 mm in diameter) by referring to the gel strength testing. When a constant shear rate is applied, increased stress can be monitored as a function of time. The force was defined as the maximum repulsive force (N/m²) when the probe was moved downward at 0.1 mm/s for 100 s into 10 mL of OVD in a centrifuge tube (29 mm in diameter). Each sample was measured three times, and the mean value was calculated.

**Results and Discussion**

In the latest study, we have evaluated the following physical properties of dispersive OVDs as corneal wetting agents in the Wet Shell Technique: spreadability, smoothness, and retention durability on the corneal surface. Among dispersive OVDs, Shellgan and Viscoat showed near-ideal properties as corneal wetting agents, which ophthalmologists desire. Moreover, the retention durability of OVDs in the eye is one of the most important properties of OVDs for corneal endothelium protection during intraocular surgery. To greater understand this property of dispersive OVDs, we examined the intraocular behavior of OVDs in this study.

Firstly, we compared the ex vivo behavior of OVDs in the porcine anterior chamber during aspiration through an IA tip or a PEA tip. The dispersive OVD, Shellgan or Viscoat, remained in the eye after a 2-min treatment, whereas the cohesive OVD, Opegan-Hi, was almost completely removed within 7 s (Fig. 1).

Although such ex vivo experiments cannot be faithfully reproduced in real surgery, our results seemed to simulate the intraocular behavior of cohesive and dispersive OVDs under turbulent flow conditions as previously reported. By using area of fluorescence as a semi-quantitative measure, we determined that the remaining amount of Shellgan in the anterior chamber was higher than that of Viscoat (Fig. 1). This is the first study to compare the removability of Shellgan and Viscoat in the eye directly. Other OVDs have been evaluated in previous reports.

The intraocular retention and ocular surface behaviors of Shellgan and Viscoat showed the same tendency. As shown in Table 2, we previously used a texture analyzer to evaluate OVD detachment force, which is as an index of the behavior of OVDs in the eye. However, the different behaviors in the eye or on the corneal surface of Shellgan and Viscoat cannot be explained only by the detachment force, which had almost the same value for both OVDs. In other words, we considered that unprecedented evaluation was necessary to understand OVD retention behavior more accurately.

To understand the retention behavior of dispersive OVDs, we focused on an alternative index of detachment force. We

<table>
<thead>
<tr>
<th>OVD Distributor</th>
<th>OVD</th>
<th>Apparent viscosity (Pa·s) at each shear rate (1/s)</th>
<th>Content</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HA</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Opegan® Santen (Japan)</td>
<td>1</td>
<td>1100 — —</td>
<td>5.4</td>
</tr>
<tr>
<td>Oplead® Senju (Japan)</td>
<td>1</td>
<td>1700 — —</td>
<td>4.9</td>
</tr>
<tr>
<td>3% HA Homemade</td>
<td>3</td>
<td>700 — —</td>
<td>37.0</td>
</tr>
<tr>
<td>Viscoat® Alcon (Switzerland)</td>
<td>3</td>
<td>700 4 20</td>
<td>67.9</td>
</tr>
<tr>
<td>Shellgan® Santen (Japan)</td>
<td>3</td>
<td>700 4 50</td>
<td>80.7</td>
</tr>
<tr>
<td>Discovisc® Alcon (Switzerland)</td>
<td>1.65</td>
<td>1600 4 20</td>
<td>223.0</td>
</tr>
<tr>
<td>Opegan-Hi® Santen (Japan)</td>
<td>1</td>
<td>2500 — —</td>
<td>131.0</td>
</tr>
</tbody>
</table>

The molecular weights (Mw) of HA or CS have already been reported. Among dispersive OVDs, Shellgan and Viscoat are dispersive OVDs.
first examined the gel strength testing that the world’s gelatin producers use to determine gelatin quality. However, we could not distinguish the difference of their gel strength (Fig. S2). Because OVDs behave as fluids described in the previous report\(^1\) and therefore do not show sufficient hardness to apply the gel strength testing. Under open conditions such as the gel strength testing, the force applied to the OVDs was absorbed by them due to the fluidity. It is suggested that the evaluation of such properties of the OVD should be performed under certain closed conditions where the force can be concentrated on the contact surface between the OVD and the measurement probe. Next, we focused on the repulsive force at which the plasticity of materials begins. Based on the above discussion, we have developed a method for determining the repulsive force in the conditions which the external force applied to the OVD is not dispersed as much as possible (Fig. S1). The new method is to measure the repulsive force generated by pushing the surface of an OVD placed in a centrifuge tube at a constant speed with a cylinder probe. By this method, we were able to evaluate the difference in repulsive force of OVDs that could not be detected by the conventional method. The fundamental texture properties of adhesive materials are tack (or detachment force), holding force, and adhesion. Considering the measurement principle, a developed method is likely to reproduce holding force.\(^1\)

Figure S1 shows a typical time–course profile of the re-
The repulsive force of OVDs increased in a time-dependent manner, and the rate of increase varied with each OVD (data not shown). We defined the force as the maximum repulsive force when the probe was moved downward into 10 mL of OVD (Fig. S1). Table 2 shows the force of OVDs and summarizes other parameters of OVDs such as detachment force obtained in previous examinations.\(^8,15\)

All evaluated OVDs showed their own repulsive force. Although Shellgan and Viscoat have almost the same composition, the maximum repulsive force of the former was 1.35 times that of the latter. The force of dispersive OVDs were positively correlated with their retention durability on the corneal surface as previously demonstrated\(^8\): the coefficient of determination (\(r^2\)) was 0.9258. Subsequently, the higher the repulsive force of OVDs, the longer the retention durability on the cornea.

Although we have not quantitatively evaluated the retention durability in the eye, we speculated that the repulsive force of OVD may also affect its intraocular behavior. Generally, differences in the repulsive force of materials can be caused by different interactions between molecules, such as van der Waals and hydrogen bonds, and molecular entanglement. Shellgan and Viscoat have no difference in composition or composition ratio, but only in the molecular weight of CS (Table 1). The difference may be caused by the difference in the interaction

<table>
<thead>
<tr>
<th>OVD products</th>
<th>Retention durability(^8) on corneal surface (%)</th>
<th>Physical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Maximum repulsive force ((\times10^4) N/m(^2))</td>
</tr>
<tr>
<td>Shellgan</td>
<td>61</td>
<td>6.5</td>
</tr>
<tr>
<td>Viscoat</td>
<td>50</td>
<td>4.8</td>
</tr>
<tr>
<td>3% HA</td>
<td>45</td>
<td>3.6</td>
</tr>
<tr>
<td>Discovisc</td>
<td>31</td>
<td>3.1</td>
</tr>
<tr>
<td>Opelead</td>
<td>27</td>
<td>1.4</td>
</tr>
<tr>
<td>Opegan</td>
<td>27</td>
<td>0.8</td>
</tr>
<tr>
<td>Opegan-Hi</td>
<td>0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Values shown in Table 2 represent the mean (\(n=3\)). The retention durability of OVDs on the corneal surface has been reported previously.\(^8\) A 0.1-mL aliquot of OVD was placed on a cornea attached to the surface of a glass slide, and the glass slide was fixed at 30°. The cornea was washed with 50 mL of distilled water four times at a constant flow rate of 1.4 mL/s, and each wash effluent was collected to measure the amount of OVD washed out. The detachment force of OVDs has been reported previously by using a texture analyzer.\(^15\) The probe was pressed downward at 0.5 mm/s. After touching a 0.1-mL OVD sample, the probe was pulled upward at 0.5 mm/s. The peak of the minimum detachment force required to separate the probe from the OVD samples was defined as the adhesive force.

Fig. 2. The Relationship between the Maximum Repulsive Force and Apparent Viscosity of OVDs

The vertical axis shows the maximum repulsive force, and the horizontal one indicates the apparent viscosities of 7 products, the viscosity at shear rate 100 s\(^{-1}\) (A), 10 s\(^{-1}\) (B), 1 s\(^{-1}\) (C), and 0.1 s\(^{-1}\) (D). (Color figure can be accessed in the online version.)
of HA–CS molecules due to van der Waals force and hydrogen bond, and the entanglement of these molecules.

Non-Newtonian fluids like various HA products have the property that their viscosity changes depending on the shear rate, and the flow changes when a force is applied to the fluid (Table 1, Fig. S3). Arshinoff has reported that the intraocular behavior of OVDs in various scenes during ophthalmic surgery may be associated with changes in their viscosity depending on the shear rate.18) In this study, we demonstrated that the viscosity at high shear rates showed a good correlation with the maximum repulsive force in each OVD: the \( r^2 \) value was 0.9658 when measuring the viscosity at 10 s\(^{-1} \) and 0.9073 at 100 s\(^{-1} \) (Fig. 2). The results suggested that OVDs with higher apparent viscosity at high shear rates might exhibit stronger retention durability in the eye. However, the intraocular behavior of OVD under high turbulence conditions such as aspiration cannot be explained only by the change in viscosity.

Although Arshinoff has suggested that viscosity may correlate with internal friction caused by the molecular attraction that resists the flow of viscous fluids, we considered that the intraocular behavior of OVD under high turbulence conditions such as aspiration cannot be explained only by the change in viscosity. A different property, known as apparent viscosity, was required to explain the mechanism of OVDs retention. The repulsive force measured in this study is likely close to that of the OVD in the eye under the conditions of flow caused by PEA and IA. We succeeded in evaluating the status of OVDs in terms of a physical characteristic value, designated maximum repulsive force. Our results suggested that the force can be a new index of OVDs resistance to external flow produced during procedures such as PEA and IA.

In conclusion, we demonstrated that maximum repulsive force is related to the retention durability of OVDs in the eye and on the cornea surface. The force can be used as an index to assess the difference in the retention durability of OVDs with the same specifications such as Shellgan and Viscoat. We supposed that the difference in OVD retention durability is likely to influence OVD usability or operability. This retention parameter provides useful information for better understanding and predicting the behavior of OVDs during ocular surgery.

**Conflict of Interest** The authors declare no conflict of interest.

**Supplementary Materials** The online version of this article contains supplementary materials.

**References**